EXHIBIT F

NeuroRx®
OFFICIAL NEWSLETTER OF THE American Society for Experimental NeuroTherapeutics
ASENT

Volume 1, Issue 4
September 2001

What's Inside

The Role of Iron in Neurodegeneration

Excessive iron accumulation has been reported in the brains of patients with Parkinson's or Alzheimer's disease, and it has been postulated that abnormal iron accumulation in the brain is neurotoxic through the generation of free radicals. However, it remains unclear whether iron-induced oxidative stress is a primary or a secondary event in the process that leads to neuronal death. Two recent reports suggest that - at least in some cases - iron toxicity may be a primary event in neurodegeneration.

Neuroferritinopathy Causative Gene Identified

In recent years, Curtis *et al* have described a previously unrecognized adult-onset neurodegenerative disease that affects the basal ganglia and is associated with iron accumulation. The disease is dominantly inherited and presents with extrapyramidal symptoms and low ferritin serum levels. Histopathology is characterized by lesions in the globus pallidus with abundant spherical inclusions containing aggregates of ferritin and iron. Additionally, axonal swellings are found throughout the brain and are immunoreactive for ubiqutin and tau. Within the brain, only the basal ganglia appear to be affected. Outside the brain, organs such as the pancreas, liver, and heart that are typically affected in iron accumulation disease, appear to function normally.

"Newly recognized neurodegenerative disease associated with iron accumulation."

Using linkage analysis and positional cloning in an extended family from Northern England, Curtis *et al*, report that the causative mutation lies in the gene encoding a subunit of ferritin. More precisely the mutation affects the carboxy terminal of the L chain of ferritin and consists of the insertion of an adenine in the gene. The same mutation was found in five apparently unrelated subjects with similar extrapyramidal symptoms and low ferritin serum levels.

Ferritin, the major iron-storage protein, is composed of 24 subunits of two types, heavy (H) and light (L). These units form a hollow sphere in which iron precipitates are sequestered. Curtis *et al.* suggest that the mutation may alter ferritin's function and stability, perhaps allowing inappropriate release of iron from the mutated protein. Ferritin is normally synthesized in the cell body where it sequesters iron. It is then transported down the axons to nerve terminals where it provides iron to the synapse. Based on the crystal structure of ferritin, the authors propose that the mutated ferritin may be less stable than normal ferritin and may release iron within the axon, causing iron-dependent oxidative damage of axons and loss of function of a number of axonal proteins. This axonally-initiated toxicity may explain why significant pathology is seen only in the central nervous system.

ASENT Mission Statement

The purpose of the American Society of Experimental NeuroTherapeutics is:

– To provide a forum for broadly defined interest areas of academia, government, and industry

concerned with the field of neurotherapeutics.

– To promote dialogue, understanding and cooperation among the interested groups.

– To develop information and seek consensus on matters germane to the organization's mission.

– To organize education and training for healthcare practitioners, biomedical scientists and officials participating in the neurotherapeutics field.

Interestingly, mice that lack iron-regulatory protein 2 and that overexpress both H and L ferritin chains show a similar pattern of neurotoxicity. In this case, axonal release of iron could be due to the degradation of overexpressed ferritin by lysosomes present in distal axons.

Hallervorden-Spatz Syndrome: Gene Defect Identified

Hallervorden-Spatz Syndrome (HSS) is a progressive, autosomal neurodegenerative disorder of childhood and adolescence. The disease usually presents with stiffness of gait and distal wasting. Muscle tone is both spastic and rigid. Reflexes are hyperactive, and the toes are usually upgoing. Dystonia is sometimes present. Pigmentary degeneration of the retina is seen in some families. In others optic atrophy is observed. The course of the illness typically spans a dozen years. Several clinical variants have been described, with relatively stereotyped courses within families, suggesting genetic heterogeneity. Diagnosis is confirmed by demonstration of increased uptake of the iron isotope ^{59}Fe by scanning the basal ganglia. Definite diagnosis requires autopsy. Olive or golden-brown discoloration of the globus pallidus is characteristic and is due to granules of an iron-containing lipopigment located inside and outside neurons. The affected tissues contain an increased amount of iron and axonal swellings.

" Neurodegenerative disease due to inborn error of pantothenate metabolism."

Using linkage analysis of an extended Amish pedigree, Zhou *et al* had previously defined an interval on chromosome 20p13 that contained the gene for HSS. They now report that the culprit gene encodes a pantothenate kinase (PANK2), an essential regulatory enzyme in the biosynthesis of CoenzymeA (CoA). HSS is the first inborn error of pantothenate metabolism

CoA is the major acyl carrier and plays a central role in intermediary and fatty acid metabolism . There could be many reasons why a PANK2 defect causes neurotoxicity. First, CoA depletion results in defective membrane biosynthesis. This could explain the retinopathy frequently observed in HSS, since rod photoreceptors continually generate membranous discs.

Second, a PANK2 defect could alter iron concentrations in the brain indirectly by affecting cysteine concentrations. Phosphopantothenate, the product of PANK2, normally condenses with cysteine in the next step in the synthesis of CoA. Phosphopantothenate deficiency leads to increased concentrations of cysteine within neurons. Not surprisingly therefore, the concentrations of cysteine have been found to be abnormally high in the globus pallidus of HSS patients.

How could increased concentrations of cysteine cause neuronal damage? Probably through the formation of free radicals. Cysteine undergoes rapid auto-oxidation in the presence of iron resulting in free radical production. In addition, iron-induced lipid peroxidation, a likely mechanism of secondary pathogenesis in HSS, is enhanced by free cysteine.

The authors conclude that it may be possible to slow the progression of HSS by therapeutically delivering compounds that bypass PANK2

and drive CoA synthesis. This study also raises the possibility that errors in pantothenate metabolism may represent a common pathway in a number of other neurodegenerative diseases.

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Sources

Curtis ARJ, Fey C, Morris CM, et al. Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease. Nature Genetics 2001; 28: 350-354.

Zhou B, Westaway SK, Levinson B. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. Nature Genetics 2001; 28: 345-349.

Reviewed by Rouault TA. Iron on the brain. Nature Genetics 2001; 28: 299-300.

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A Vaccine for Prion Disease?

A series of monoclonal antibody fragments that bind to the normal prion protein PrPC were tested in infected cell cultures expressing the abnormal prion protein PrPSC. Some, but not all fragments, were found to dramatically and dose-dependently reduce the levels of PrPSC without affecting the levels of PrPC. Duration of exposure to antibodies is critical. Cells passaged for seven days in the presence of antibody fragments had a high relapse rate and PrPSC levels returned to 50% of control (untreated culture) within seven days after removal of antibodies from the culture medium. By contrast, if cells were exposed to antibody fragments for two weeks, PrPSC levels remained undetectable even after four weeks of culture without antibody.

To confirm that PrPSC had been cleared from the cultures, CD-1 Swiss mice were inoculated with antibody-treated and untreated infected cells. Mice inoculated with antibody-treated cells were free of prion disease 265 days later, whereas mice inoculated with untreated cells had a mean incubation time of 165 days.

To explain their results, the authors propose that by binding to the normal protein PrPC on the cell surface, antibody fragments prevent the docking of PrPSC and the conversion of the PrPC to PrPSC. This blocks prion propagation. Over time (one to two weeks), residual PrPSC is eliminated through normal cellular degradation pathways. The results suggest that it may be possible to cure prion disease by developing drugs that bind critical regions on the PrPC protein. Recently, two approved drugs - the antimalarial quinacrine and the antipsychotic chlorpromazine- have been updated by the same group to block prion propagation *in vitro* (Proc. Natl. Acad. Sci. USA 2001; 98:9836). Clinical trials in patients are planned for both drugs, individually and in combination. Vaccines against prion disease may also be an alternative. The critical question remains whether the above *in vitro* results translate *in vivo* to patients.

Source: Peretz A, Williamson RA, Kaneko K, et al. Antibodies inhibit prion propagation and clear cells of prion infectivity. Nature 2001; 412: 739-743.

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a digest of disease management news

December 1999 Vol 3. No. 10

Iron Dysregulation Seen in Parkinson's

Iron levels in the substantia nigra, the site of maximal neurodegeneration in Parkinson's victims, are notably elevated. This tends to increase ferritin loading and possibly the risk of free radical-induced damage. Abnormal iron metabolism, iron-induced oxidative stress, and free radical formation affect levels of neuromelanin and hemosiderin in substantia nigra neurons, increase lipid peroxidation products and reactive oxygen species, decrease availability of glutathione and other antioxidants, and decrease mitochondrial electron transport. The interaction between iron and neuromelanin causes accumulation of iron and cytotoxic species, which eventually leads to neuronal death. This dysregulation of iron metabolism is seen in both early- and late-onset Parkinson's.

These findings indicate that in addition to the dopamine agonists, monoamine oxidase-B inhibitors, glutamate antagonists, catechol O-methyltransferase inhibitors, and free radical scavengers currently used to treat Parkinson's, agents that chelate iron or otherwise retard the formation or accumulation of iron-associated toxic substances may provide significant neuroprotection and delay disease progression.

Trivalent metal ions (Fe^{3+}, Al^{3+}, Cr^{3+}, In^{3+}, Ga^{3+}, and La^{3+}) have been identified to cause an ATP-mediated cellular calcium influx, creating an intracellular calcium overload eventually leading to cell death. This provides yet another possible contributing mechanism by which iron causes neurodegeneration.
By contrast, a zinc deficiency is associated with Parkinson's disease. Levels of zinc in the cerebrospinal fluid of victims are substantially lower than those without Parkinson's. The enzyme superoxide dismutase contains zinc as an essential component. It is normally present in high concentrations in the substantia nigra where it scavenges free radicals. It catalyzes the dismutation of superoxide anions to hydrogen peroxide and oxygen thus exerting a neuroprotective effect. Zinc supplementation produces significant increases in superoxide dismutase activity.

Normal metabolism of dopamine results in production of

peroxide, superoxide, and hydroxyl radicals, all reactive oxygen species. It also results in the formation of reactive quinones similar to those found in environmental toxins that can damage cellular macromolecules covalently. This suggests a more direct role of dopamine in neurodegeneration. This process is facilitated by iron and manganese ions, further implicating those metals in the pathophysiology of this disease.

Sources:

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• Jellinger KA. The role of iron in neurodegeneration: prospects for pharmacotherapy of Parkinson's disease. *Drugs Aging.* 1999;2:115-140.
• Vymazal J, Righini A, Brooks RA, Canesi M, Mariani C, Leonardi M, Pezzoli G. T1 and T2 in the brain of healthy subjects, patients with Parkinson disease, and patients with multiple system atrophy: relation to iron content. *Radiology.* 1999;211(2):489-495.
• Bartzokis G, Cummings JL, Markham CH, Marmarelis PZ, Treciokas LJ, Tishler TA, Marder SR, Mintz J. MRI evaluation of brain iron in earlier- and later-onset Parkinson's disease and normal subjects. *Magn Reson Imaging.* 1999;2:213-222.
• Stokes AH, Hastings TG, Vrana KE. Cytotoxic and genotoxic potential of dopamine. *J Neurosci Res.* 1999;55(6):659-665.
• Anghileri LJ, Thouvenot P. ATP in cellular calcium-overload by trivalent metal ions. *Biol Trace Elem Res.* 1998;62 (1-2):115-122.
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• Jiménez-Jiménez FJ, Molina JA, Aguilar MV, Meseguer I, Mateos-Vega CJ, González-Muñoz MJ, de Bustos F, Martínez-Salio A, Ortí-Pareja M, Zurdo M, Martínez-Para MC. Cerebrospinal fluid levels of transition metals in patients with Parkinson's disease. *J Neural Transm.* 1998;105(4-5):497-505.

BACK

Iron in the Brain?

What are the effects of increased iron levels in the brain?

Could it be connected: To Alzheimers? To Parkinsons? To learning disabilities such as ADD, ADHD?? To other neurodegenerative disorders? Seizures, Strokes, Downs syndrome?

Click on the titles below to read studies, abstracts & links, which consider these possibilities.

- **A histochemical study of iron, transferrin, and ferritin in Alzheimer's diseased brains.**
  J Neurosci Res 1992 Jan These data strongly suggest a disruption in brain iron homeostasis in Alzheimer's disease as demonstrated by alterations in the normal cellular distribution of iron and the proteins responsible for iron regulation.

- **Alterations in the interaction between iron regulatory proteins and their iron responsive element in normal and Alzheimer's diseased brains**
  Cell Mol Biol (Noisy-le-grand) 2000 Jun An increase in iron without proper sequestration can increase the vulnerability of cells to oxidative stress. Oxidative stress is a component of many neurological diseases including Alzheimer's.

- **A quantitative analysis of isoferritins in select regions of aged, parkinsonian, and Alzheimer's diseased brains.** J Neurochem. 1995 Aug; The brain requires a ready supply of iron for normal neurological function, but free iron is toxic. Consequently, iron bioavailability must be stringently regulated. Recent evidence has suggested that the brain iron regulatory system is dysfunctional in neurological disorders such as Alzheimer's and Parkinson's diseases.

- **Are hereditary hemochromatosis mutations involved in Alzheimer disease?**
  The possibility that HFE mutations are important new genetic risk factors for AD should be pursued further. Am J Med Genet 2000 Jul

- **Body iron stores and early neurologic deterioration in acute cerebral infarction**
  Neurology 2000 Increased body iron stores may contribute to stroke progression by enhancing the cytotoxic mechanisms in cerebral ischemia American Academy of Neurology

- **Can the controversy of the role of aluminum in Alzheimer's disease be resolved?**
  J Toxicol Environ Health 1996 Aug 30 At first glance, this is about aluminum-but keep reading.

- **Cellular distribution of transferrin, ferritin, and iron in normal and aged human brains.**
  J Neurosci Res 1990 Dec

- **Cellular management of iron in the brain** J Neurol Sci 1995 Dec Changes in the cellular distribution of iron and its associated regulatory proteins occur in Alzheimer's disease.

- **Central nervous system and eye** Barton 2000, p. 211

- **Chemistry and biology of eukaryotic iron metabolism.** Int J Biochem Cell Biol. 2001 Oct Department of Physiology and Biophysics, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY A surprising connection between iron metabolism and Friedreich's ataxia has been uncovered. It is no

exaggeration to say that the new understanding of iron metabolism in health and disease has been explosive, and that what is past is likely to be prologue to what is ahead.

- **Clinical report of three patients with hereditary hemochromatosis and movement disorders** HH should be investigated more systematically in patients with movement disorders. Mov Disord 2000 Nov

- **Desferrioxamine and vitamin E protect against iron and MPTP-induced neurodegeneration in mice.** J Neural Transm 1997 Our data suggested that: (1) iron may induce neuronal damage and thus excessive iron in the brain may contribute to the neuronal loss in PD; (2) iron chelators and antioxidants may serve as potential therapeutic agents in retarding the progression of neurodegeneration.

- **Dietary Iron Supplements - Use or not to use?**
Nutrition Today James R. Connor John L. Beard 05-06-1997 There is little reason to support a general need for iron supplementation in the diet at any age. Perhaps this article and review of supplementation pros and cons should conclude with a new interpretation of an old saying: "It is better to wear out than to rust out;" don't expose your system to more iron than it needs. [assoc. with MS, AD, PD?]

- **Dopamine, 6-hydroxydopamine, iron, and dioxygen--their mutual interaction and possible implication in the development of Parkinson's disease** Biochim Biophys Acta 1996 Aug 23

- **Excessive iron accumulation in the brain: a possible potential risk of neurodegeneration in Parkinson's disease.** J Neural Transm 1997 Excessive iron accumulation in the brain, however, is a potential risk for neuronal damage, which may promote by triggering factor(s). This supports the hypothesis that excessive cerebral iron may contribute to the aetiology of Parkinson's disease (PD).

- **Existing and emerging mechanisms for transport of iron and manganese to the brain.**
J Neurosci Res 1999 Apr 15 These metals are treated together because they appear to share several transport mechanisms. In addition, several neurological diseases such as Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease are all associated with Fe mismanagement in the brain, particularly in the striatum and basal ganglia.

- **Fibromyalgia, Chronic Fatigue, Alzheimer's: Causes (?) and Treatment**
by Darrell Stoddard Copyright 2001

- **FOR MANY ELDERLY AMERICANS WHO HAVE EXCESS IRON IN THEIR BODY, TAKING IRON SUPPLEMENTS IS UNNECESARRY AND MAY BE DANGEROUS**
The American Society for Nutritional Sciences The American Society for Clinical Nutrition 9650 Rockville Pike, Bethesda, Maryland 20814-3998 March 2001

- **Fried reich's Ataxia Fact Sheet** ......the finding of abnormally high levels of iron in the heart tissue of people with Friedreich's ataxia National Institute of Neurological Disorders and Stroke

- **Hemochromatosis: A Common, Rarely Diagnosed Disease**
By Vincent J. Felitti, MD, FACP Commentary by David Baer, MD, FACP. Hemochromatosis is the most common, life-threatening genetic disorder in North America, yet most physicians have never personally diagnosed a case: all see an unrecognized case in their offices every two weeks.

- **Hereditary haemochromatosis: a case of iron accumulation in the basal ganglia associated with a parkinsonian syndrome:** J Neurol Neurosurg Psychiatry 1995 Sep Hereditary haemochromatosis should be considered in the differential diagnosis of parkinsonian syndromes, because complications of iron induced organ injury may be prevented by phlebotomy.

- **High Iron May Mean Worsening Stroke** But U.S. specialists say Spanish study is not the last word By

Adam Marcus HealthScout Reporter MONDAY, April 24, 200 (HealthScout) -- High iron levels in the blood may be an important factor in figuring out who will fare worse after a stroke. Patients with very high iron levels were about 80 percent more likely to have a type of brain damage that eroded still more after a stroke than those with levels nearly half as great. The brains of the stroke victims with less iron stabilized or grew better, according to a new study by Spanish researchers in this month's *Neurology*.

- **Increased basal ganglia iron levels in Huntington disease**
  The data suggest that increased iron levels may be related to the pattern of neurotoxicity observed in HD. Reducing the oxidative stress associated with increased iron levels may offer novel ways to delay the rate of progression and possibly defer the onset of HD. *Arch Neurol. 1999*

- **Increased cerebral iron uptake in Wilson's disease: a 52Fe-citrate PET study.** J Nucl Med 2000 May Toxicity of abundant copper is the main cause of brain and liver tissue damage in patients with Wilson's disease (WD). However, there is also evidence of a disturbed iron metabolism in this genetically determined disorder.

- **Influence of ferritin levels on LDL cholesterol concentration in women.**
  Res Commun Mol Pathol Pharmacol. 1997 Nov Both modified or oxidized LDL and elevated LDL concentration are regarded as risks for atherosclerosis and ischemic heart disease, suggesting that higher body iron is important in this process.

- **In vitro studies of ferritin iron release and neurotoxicity** J Neurochem 1998 Jun These results suggest that ferritin iron release contributes to free radical-induced cell damage in vivo.

- **Iron as catalyst for oxidative stress in the pathogenesis of Parkinson's disease?**
  Life Sci 1999

- **Iron, Atherosclerosis, and Ischemic Heart Disease**
  Arch Intern Med. 1999; Objective To review the epidemiological and experimental data concerning iron and the development of atherosclerosis and ischemic heart disease.

- **Iron catalyzed oxidative damage, in spite of normal ferritin and transferrin saturation levels and its possible role in Werner's syndrome, Parkinson's disease, cancer, gout, rheumatoid arthritis, etc.** Med Hypotheses 2000 Sep the disease is often overlooked by physicians, until several organs have been damaged permanently (heart, liver, brain, pancreas, kidneys, spleen, etc.). Moreover, since ferritin, transferrin saturation and hematocrit levels are not directly related to cellular iron levels, and since excess iron can wreak havoc in the cell, we can conclude that there is a need for a better way to evaluate intracellular iron levels and especially the intracellular free iron levels by a non-invasive technique.

- **Iron Imbalance in the Brain is a factor in Many Neurological Disorders** James R. Connor, Ph.D. speaker at the International Patient Conference, Iron Disorders Institute October 2001

- **Iron Loading and Disease Surveillance**
  Eugene D. Weinberg Indiana University, Bloomington, Indiana Emerging Infectious Diseases Journal, National Center for Infectious Diseases, Centers for Disease Control and Prevention. Excessive iron in specific tissues and cells (iron loading) promotes development of infection, neoplasia, cardiomyopathy, arthropathy, and various endocrine and possibly neurodegenerative disorders.

- **Iron overload and psychiatric illness** Can J Psychiatry 1994 Feb, Dr. Paul Cutler. These cases indicate a need to be aware that disordered iron metabolism is a somatic cause of psychiatric illness and that there is clinical improvement upon lowering elevated iron levels in patients with iron overload.

- **Iron overload, oxidative stress, and axonal dystrophy in brain disorders**
  Pediatr Neurol 2001 Aug

- **Iron overload without the C282Y mutation in patients with epilepsy.** J Neurol Neurosurg Psychiatry. 2001 Apr; To test the hypothesis that iron overload predisposes to epilepsy, transferrin saturation in 130 patients with epilepsy and sex and age matched 128 control subjects without epilepsy were studied.

- **Iron Problems May Lead to Parkinson's**
  Mouse study shows direct link. By Julia McNamee Neenan *HealthScout Reporter 1-30-01*

- **Iron-storing disorders shed light on Parkinson's**
  By Emma Hitt,PhD Health Talk with Dr. Bob Martin July 2001

- **Iron uptake by glial cells.** The data reinforces the likelihood that iron uptake by nervous tissues is transferrin-mediated. Neurochem Res 1985 Dec.

- **Is Alzheimer's disease iron overload of the brain?**
  Alzheimer's Research Journal VOLUME: 03 ISSUE: 01 PAGES: 69-72

- **Is hemochromatosis a risk factor for Alzheimer's disease?** Journal of Alzheimer's Disease Volume 3, Number 5, October 2001 *Pages 471-477* J. R.Connor, E. A. Milward, S. Moalem, M. Sampietro, P. Boyer, M. E.Percy, C. Vergani, R. J. Scott, M. Chorney *(communicated by Paolo Zatta)*

- **Is Parkinson's disease a progressive siderosis of substantia nigra resulting in iron and melanin induced neurodegeneration?** Acta Neurol Scand Suppl 1989 Thus, without evoking environmental neurotoxins, the excessive accumulation of free iron in the SN and "melanin-trap" could be the trigger for accelerated cell death and Parkinsonism.

- **Is Parkinson's disease the heterozygote form of Wilson's disease: PD = 1/2 WD?**
  Med Hypotheses 2001 Feb

- **Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice.** Proc Natl Acad Sci U S A. 2001 Jul 17 In conclusion, our results highlight the role of hepcidin as a key regulator of iron homeostasis. We propose hepcidin as a novel candidate gene that, when mutated, could be involved in abnormal regulation of iron metabolism and development of HH. Finally, this new murine model of iron overload disease appears to be a suitable animal model for testing new therapeutic approaches for prevention and correction of the iron storage in HH as well as for the understanding of iron homeostasis.

- **Low Molecular Weight Iron in Cerebral Ischemic Acidosis In Vivo** Stroke 1998;29:487-493 AHA. This enlightening study constitutes a starting point for future investigations focusing on the effect of cerebral ischemia on the cellular and molecular factors regulating free intracellular iron.

- **Low penetrant hemochromatosis phenotype in eight families: no evidence of modifiers in the mhc region.**
  Blood Cells Mol Dis. 2001 Mar-Apr We investigated eight families including C282Y homozygous relatives showing no clinical signs of the disease, in addition to the hemochromatosis patients.

- **MRI evaluation of brain iron in earlier- and later-onset Parkinson's**
  Magn Reson Imaging 1999 Feb The FDRI results suggest that disregulation of iron metabolism occurs in PD and that this disregulation may differ in earlier- versus later-onset PD.

- **National Institute for Neurological Disorders and Stroke** all mention iron involvement in the brain:

Narrative from the FY2001 Congressional Justification for Non-AIDS Activities

Parkinson's Disease: A Research Planning Workshop
Parkinson's Disease - Hope Through Research
NINDS Zellweger Syndrome Information Page

- **Parkinson's Disease as Multifactorial Oxidative Neurodegeneration:** Implications for Integrative Management Parris M. Kidd, PhD

- **Parkinson's Disease: A Research Planning Workshop** National Institute of Neurological Disorders and Stroke Iron levels are high in the brain, and iron promotes reactions that create free radicals.

- **Parkinson's Disease as Multifactorial Oxidative Neurodegeneration: Implications for Integrative Management** Alternative Medicine Review - Volume 5, Number 6, December 2000, Parris M. Kidd, PhD. The SN is uniquely vulnerable to oxidative damage, having a high content of oxidizable dopamine, neuromelanin, polyunsaturated fatty acids, and iron, and relatively low antioxidant complement with high metabolic rate.

- **Parkinson's Disease - Hope Through Research** National Institute of Neurological Disorders and Stroke: Evidence that oxidative mechanisms may cause or contribute to Parkinson's disease includes the finding that patients with the disease have increased brain levels of iron, especially in the substantia nigra.

- **PULLING IRON OUT OF THE FIRE** by Shelly Morrow. This article appeared in the Sept/Oct 2000 issue of Arthritis Today, published by the Arthritis Foundation, Inc.,

- **Recent advances in disorders of iron metabolism: mutations, mechanisms and modifiers** Hum Mol Genet 2001 Oct 1

- **Recent scientific advances in neurogenetics, Friedreich's Ataxia, iron & yeast** A brain imaging technique has shown that iron levels are indeed selectively elevated in the brains of patients with Friedreich's, suggesting that targeting iron metabolism may help treat the disease.

- **Regional distribution of iron and iron-regulatory proteins in the brain in aging and Alzheimer's disease** J Neurosci Res 1992 Feb The observations in this study are consistent with our general hypothesis that iron homeostasis is disrupted in the aging brain and the alterations in iron-regulatory proteins are exacerbated in Alzheimer's disease.

- **Regional distribution of iron, transferrin, ferritin, and oxidatively-modified proteins in young and aged Fischer 344 rat brains** Neuroscience 1997 Jul Iron dysregulation in the brain is thought to contribute to the oxidative damage seen in neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.

- **Regulation of Expression of Iron Binding Proteins in the Nervous System,** James R. Connor, Ph.D., University of California, Berkeley, 1981; Postdoctoral Training, Boston University School of Medicine, 1981-1983 The goal of this laboratory is to learn how the brain maintains an appropriate balance and ready supply of iron and what happens to normal brain function when an imbalance of iron occurs. Our research efforts are directed at the proteins which regulate iron bioavailability. Our data had led to the discovery that the brain's ability to mobilize iron is diminished in Alzheimer's Disease and in specific regions of the brain in Parkinson's Disease.

- **Risk of disease in siblings of patients with hereditary hemochromatosis** Digestion 2001

- **'Rusty' nerve endings may cause diseases** Ananova. November 2000 Diseases such as Parkinson's and Alzheimer's may be caused when nerve endings in the brain turn "rusty", according to new research.

- **Search hemochromatosis From: Oct 1999 In Journals: Neurology**
4 articles returned that require subscriptions

- **T1 and T2 in the brain of healthy subjects, patients with Parkinson disease, and patients with multiple system atrophy: relation to iron content** Radiology. 1999; In conclusion, the results of this study confirm and extend earlier reports of the linear relation between MR signal and iron content in iron-containing deep nuclei. This study is more robust in that both T1 and T2 changes are used, providing a more specific and accurate determination of changes in iron content and form

- **The hemochromatosis gene affects the age of onset of sporadic Alzheimer's disease** HFE mutations may anticipate AD clinical presentation in susceptible individuals. Neurobiol Aging 2001 Jul-Aug

- **The HFE CYS282Tyr polymorphism is associated with cardiovascular mortality.**
Roest M, Schouw Yvd, B. de Valk BD, Marx JJM, Tempelman M, de Groot P, Sixma J, Banga JD. Presented at the July 1998 meeting of the European Iron Club. Conclusions: Heterozygosity for HH is associated with increased risk of cerebrovascular and total cardiovascular mortality, in particular in combination with hypertension and smoking. Long term exposure to minimal iron overload may enhance atherosclerosis.

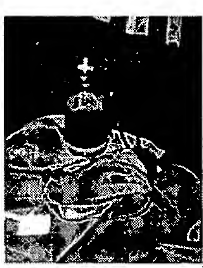
- **The possible role of iron in the etiopathology of Parkinson's disease** Mov Disord 1993 The recently described pathology of PD supports the view for a state of oxidative stress in the substantia nigra (SN), resulting as a consequence of the selective accumulation of iron in SN zona compacta and within the melanized dopamine neurons.

- **The role of iron in neurodegeneration: prospects for pharmacotherapy of Parkinson's disease**
Drugs Aging 1999 Feb;Although the aetiology of Parkinson's disease (PD) and related neurodegenerative disorders is still unknown, recent evidence from human and experimental animal models suggests that a misregulation of iron metabolism, iron-induced oxidative stress and free radical formation are major pathogenic factors.

- **Transferrin and iron in normal, Alzheimer's disease, and Parkinson's disease brain regions.**
J Neurochem 1995 Aug Department of Medicine, Sinai Hospital, Detroit, MI. The altered relationship between iron and transferrin provides further evidence that a disturbance in iron metabolism may be involved in both disorders.

- **Transferrin C2 and Alzheimers** Med Hypotheses 1995 Apr We hypothesize that Alzheimer's disease is caused by free radical damage to membranes of endocytic vesicles due to defective binding of iron and aluminium by Tf C2.

- **Zellweger Syndrome Information Page**
National Institute of Neurological Disorders and Stroke The most common features of Zellweger syndrome include an enlarged liver, high levels of iron and copper in the blood, and vision disturbances.



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